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Protective autoimmunity against the enemy within: fighting glutamate toxicity.

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Glutamate, a key neurotransmitter, is pivotal to CNS function. Alterations in its concentration can be dangerous, as seen for example in acute injuries of the CNS, chronic neurodegenerative disorders and mental disorders. Its homeostasis is attributed to the efficient removal of glutamate from the extracellular milieu by reuptake via local transport mechanisms. Our recent studies suggest that glutamate, either directly or indirectly, elicits a purposeful systemic T-cell-mediated immune response directed against immunodominant self-antigens that reside at the site of glutamate-induced damage. We suggest that the harnessed autoimmunity (which we have termed 'protective autoimmunity') helps the resident microglia in their dual function as antigen-presenting cells (serving the immune system) and as cells that clear the damaged site of potentially harmful material (serving the nervous system). The interplay between glutamate and an adaptive immune response illustrates the bidirectional dialog between the immune and nervous systems, under both physiological and pathological conditions. These results point to the possible development of a therapeutic vaccination with self-antigens, or with antigens cross-reactive with self-antigens, as a way to augment autoimmunity without inducing an autoimmune disease, thus providing a safe method of limiting degeneration. This approach, which boosts a physiological mechanism for the regulation of glutamate, and possibly also that of other self-compounds, might prove to be a feasible strategy for therapeutic protection against glutamate-associated neurodegenerative or mental disorders.

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